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Time from Sexually Transmitted Infection Acquisition to Pelvic Inflammatory Disease Development: Influence on the Cost-Effectiveness of Different Screening Intervals

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ABSTRACT

Objectives: To prevent pelvic inflammatory disease (PID), some experts recommend screening for sexually transmitted infection (STI) every 12 months, with more frequent screening suggested in higher-risk women. Nevertheless, the time from STI acquisition to PID development, possibly an important factor to consider in screening interval choice, is unknown and its influence on the effectiveness and cost-effectiveness of screening is unclear.

Methods: Using a Markov model, we estimated PID cases averted and the incremental cost-effectiveness resulting from 6- or 12-month screening strategies for high-risk young women (6%/year infection risk, 2.8%/year PID risk with 12-month screening) while varying PID development time from 1 to 12 months after initial infection. Lower-risk women and alternative parameter values were examined in sensitivity analyses.

Results: Relative to 12-month screening, 6-month screening decreases PID cases from 6.0% (1 month development time) to 19.4% (12 months); the incremental cost per quality-adjusted life-year (QALY) gained compared with the other strategies varies from $16,600 (12 months development time) to $31,800 (1 month) for high-risk women. In lower-risk women, every 6-month screening is more economically unfavorable, with greater costs per QALY gained at shorter PID development time.

Conclusion: From a cost-effectiveness standpoint, uncertainty about PID development time is not a significant factor in choosing a screening interval in high-risk women, but could be important in lower-risk groups. Significant increases in PID cases averted occur with more frequent screening when PID development time is lengthened, which may allow estimation of this interval through the use of more sophisticated modeling techniques.

Keywords: cost-effectiveness analysis, decision analysis, pelvic inflammatory disease, sexually transmitted disease.

Introduction

Pelvic inflammatory disease (PID), caused most frequently by sexually transmitted infection (STI), is a major cause of disability in young women, leading to infertility, ectopic pregnancy, and chronic pelvic pain [1]. PID occurs because of migration of pathogens (most commonly chlamydia and gonorrhea) to the upper female genital tract, provoking tubal inflammation and subsequent tissue damage [2].To prevent PID, screening for STI is recommended, but the optimal screening interval is unclear [3,4]. The Centers for Disease Control and Prevention (CDC) recommends screening sexually active adolescent women for chlamydia "at least annually" and annual screening for women aged 20 to 25 years [3], while the US Preventive Services Task Force suggests every 6- to 12-month screening for previously infected women, because of high rates of reinfection [4]. Other authors recommend twice yearly screening for women less than 25 years old [5] with consideration for routine gonorrhea screening in high-risk young women [6].

The costs and benefits of STI screening may be influenced by a variety of infection characteristics. Many women develop infections and carry them (asymptomatically or symptomatically) for prolonged periods of time [3]. Because screening for STI has been shown to be beneficial for the individual infected woman in preventing PID [4,7], there must be some time interval between initial infection and PID development; otherwise screening would not be useful for the infected woman if PID immediately followed infection. Many previous cost-effectiveness models have not specifically addressed development time [8–11], while another assumes progression to PID within 6 months of infection [12]. Mechanisms for PID development in infected women are unclear, with the prolonged nature of untreated infections and reinfection rates both likely contributing to the onset of PID, among other factors

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[2,13,14]. Screening-initiated treatment of STI could thus prevent PID in the infected woman by interrupting the damaging effects of: (1) persistent infection; (2) subsequent infections or reinfections in women with untreated or belatedly treated prior infections; or (3) the combination of STI and concurrent non-sexually transmitted vaginal infection [15]. The time interval between STI and PID development may be a function of all these factors, among others. Whatever the mechanism, the PID development time remains unmeasured, but could be an important factor to consider in choosing STI screening intervals. For example, if the PID development time is relatively short, screening at shorter intervals could be more favorable than at longer intervals. On the other hand, if a long delay between STI acquisition and PID development exists, then screening might be needed less often. Measurement of this interval is complicated by the frequency of asymptomatic infections and of asymptomatic PID, the role of mixed infections in the etiology of PID, as well as the possible influences of the menstrual cycle and of behaviors, such as douching [13,15–24].

There is a tension between the level of biological realism incorporated into a model and the model's complexity and data requirements. Since the time between infection and PID development may be an important factor in screening interval choice but has been difficult to measure, its effect may be estimated through mathematical modeling. In this analysis, we examine how variation of PID development time changes the effectiveness and cost-effectiveness of 6- and 12-month screening intervals, seeking to understand the importance of measuring PID development time and including it in models of PID.

Methods

We constructed a Markov decision model for the natural history of PID, with the ability to vary PID development time. Using this model, we estimated the proportion of PID cases prevented and the incremental cost per quality-adjusted life-year (QALY) gained by combined chlamydia and gonorrhea screening, comparing three strategies: no screening, every 6-month screening, and every 12-month screening, while examining the impact of varying PID development time from 1 to 12 months. Our baseline analysis examined high-risk young women, the focus of present STI screening programs, over a 4-year time horizon. The analysis follows the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine, taking a societal perspective and discounting future costs and benefits at 3% per year [25].

We made several simplifying assumptions in our model. Chlamydial and gonococcal etiologies for PID were considered together, rather than separately, thus assuming that acute infection for either is the same and PID development time was similar for each. Because of both the theoretical nature of the model and the lack of reliable data, we also considered all possible causes of progression (i.e., prolonged infection, subsequent infection or reinfection, or concurrent non-STI) from infection to PID together, modeling the likelihood of progression based on the GYN Infections Follow-Through (GIFT) Study, a prospective cohort study that followed adolescents and young women at STI high risk over an average of 4 years [15,23]. Based on the GIFT Study, we used a 4-year time horizon in our base-case analysis, but considered longer time horizons in sensitivity analyses. We assumed no deaths from acute PID or its complications, slightly biasing the model against screening. We modeled all PID complications as a single state, and assumed that PID complications were not cured over the model time horizon. As in the GIFT Study, we define high-risk women, using a risk stratification paradigm [26], as those with a score ≥ 3, where aged 24 years or more = 1, black race = 2, never pregnant = 1, two or more sexual partners = 1, douches at least once a month = 1, and any prior STI = 2.

Figure 1 is a schematic representation of the model. The Markov cycle length was 1 month. Hypothetical cohorts of 18-year-old women began in the well state. Based on infection risks and the likelihood of symptomatic infection, they could transition to the asymptomatic or symptomatic infection state. Asymptomatic infections could become symptomatic over time. Infected women transitioned to PID based on the time varying monthly risk of progression to PID. Similar to infection, PID was modeled as symptomatic or asymptomatic, with the possibility of asymptomatic PID becoming symptomatic (estimated at 1% per month, varied from 0 to 10% in sensitivity analyses). PID of either type carried the same risk of complications. Women could recover from infection or from PID because of treatment after screening or after presentation with symptomatic illness. As reported in the literature, infections could also resolve spontaneously [27,28]; we assumed identical spontaneous resolution rates for chlamydia and gonorrhea, possibly biasing against screening. Women were subject to reinfection and rescreening once treated or spontaneously cured. Women in all health states faced a small risk of death from other causes, based on the US life tables [29].

Probabilities, costs, and utilities used in our model are shown in Table 1. In our model, 21.9% of our population of high-risk women became infected over 4 years (6.0% per year) in the baseline analysis [5,6,12,23,30]. Thirty percent of infections were symptomatic and 70% of symptomatic infections were treated adequately. Of the women with uncured symptomatic infections, 30% developed PID in the first month after infection [9]. In all other infected women, the interval between infection and PID development was varied, with the model calibrated so that a 10.9%

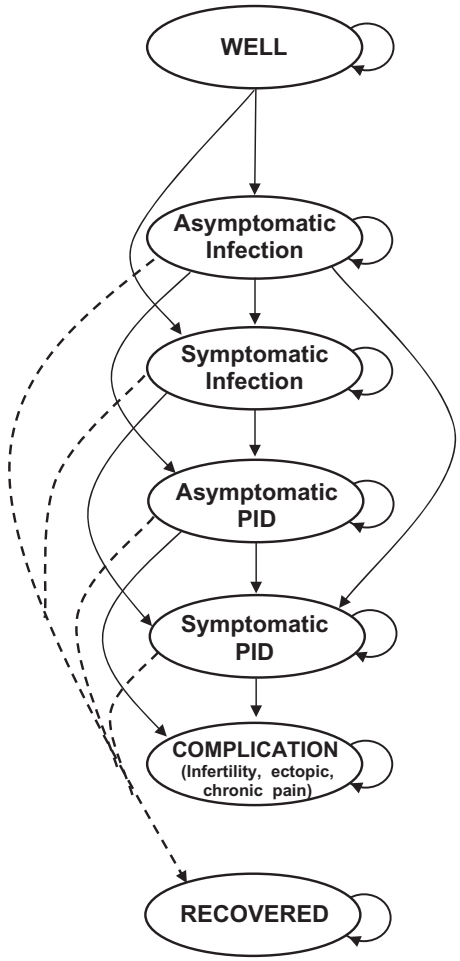

Figure 1 The Markov model. The Markov cycle length is 1 month. PID, pelvic inflammatory disease.

PID risk was observed over 4 years (2.8% per year) when a 12-month screening interval was in place, as was seen in the GIFT Study [15,23], which is consistent with rates seen in other populations of high-risk young women [7,22,31]. In sensitivity analyses, we also examined scenarios where symptomatically infected women had the same PID development intervals as the remainder of the population, where women were followed over a 10-year time horizon, and where screening was begun on 15-year-olds (rather than 18-year-olds). Women with PID had a 25% risk of chronic complications [1,32,33]. Screening and treatment costs included office visits costing $40 each [34], one for screening and a second for treatment, testing costs (DNA amplification assay for *N. gonorrhoeae* and *C. trachomatis*, baseline $25, range $10–40 [10,12]), and medication costs. Also included were the indirect costs of seeking or receiving care (2 hours for each office visit), based on the US hourly wage rates for non-farm workers [35]. A 5% risk of requiring care for medication side effects, costing $49 [12], was also included in infection treatment costs. Women who screened positive for chlamydia were treated for chlamydia with azithromycin, costing $28; those screening positive for gonorrhea were treated for both gonococcus and chlamydia with azithromycin and ciprofloxacin, costing a total of $34 [36]. Symptomatic infections of either type were treated with ceftriaxone 125 mg intramuscularly and azithromycin, costing $42 [36]. Baseline costs for screening and infection treatment were set relatively high to bias against more frequent screening. The cost of treating symptomatic PID was varied widely in sensitivity analyses based on several cost data sources [9,12,37–39] and a variety of inpatient versus outpatient treatment scenarios. The base-case value for PID treatment costs, including the cost of complications, was the discounted average lifetime cost of PID calculated by Yeh et al. [38] inflated to 2004 US dollars using the Consumer Price Index [40]. Utilities were obtained from the literature [41,42]. Screening for chlamydia and gonorrhea was sensitive and very specific [14].

In the baseline analysis, we represented intervals between asymptomatic infection and PID development as normal distributions centered on a mean, which ranged from 1 to 12 months based on mean chlamydia duration estimates of approximately 1 year in untreated women [12,27]: the distributions for development time of 3, 6, and 9 months are shown in Figure 2a. These distributions represent the time varying risk of progression from infection to PID for each development time considered. Similar distributions were used for other development time from 1 to 12 months in our baseline analysis, but are not shown. Distributions were then scaled to produce a 10.9% risk of PID [15,23] over 4 years when a 12-month screening program was in place (Fig. 2b). We examined all parameters in one-way sensitivity analyses, and selected parameters in multiway sensitivity analyses. In addition, we examined alternative screening strategies and model assumptions in structural sensitivity analyses.

Results

In the baseline analysis, more PID cases are avoided with more frequent screening when PID development time is longer, as is expected. If PID develops on average in 1 month, the relative decrease in PID cases is 6.0% for 6-month compared with 12-month screening, increasing to 19.4% when PID development time is 12 months. Nevertheless, cost-effectiveness analysis results are less sensitive to variation of PID development time in our base-case analysis of high-risk women, as summarized in Figure 3. The incremental cost-effectiveness ratio for 6-month screening compared with no screening is $31,800 per QALY gained when the mean time to PID is 1 month (0.014 QALY's

Table 1 Parameter values used in the baseline analysis and ranges examined in sensitivity analyses

Parameter	Baseline value	Range	Reference
Infection			
Likelihood (%/year)	6.0	2.5–15	5,6,12,23,30
% Symptomatic	30	0–50	3,41,44
% Treated	70	0–100	16,17,30,41,45,46
Treatment effectiveness (%)	96	94–100	12,47
Spontaneous cure (%/year)	54	40–70	27,28,32
Gonorrhea relative likelihood (%)	19	5–30	32
PID			
Likelihood (%/year)	2.8	1–5	15,16,23,24
% Symptomatic	40	0–100	13,22
% Treated	70	50–100	16,17,45
Treatment effectiveness (%)	60	40–80	24,48
% PID complication	25	10–40	1,33
Screening (%)			
Sensitivity	90	65–96	14
Specificity	99	99–100	14
Screening adherence	60	30–90	49
Treatment adherence	60	30–90	9,50
Costs ($)			
Screening	81	20–100	9,10,12,14,34,35
Infection treatment	87	35–100	9,10,12,34–36
PID treatment	2359	269–5000	9,12,37–39
Indirect (per hour)	16	0–40	35
Utility			
Infection (symptomatic)	0.9	0.8–0.99	41,42
PID (symptomatic)	0.65	0.5–0.8	41,42
Complication	0.6	0.4–0.8	41,42

PID, pelvic inflammatory disease.

gained at a cost of $444) and decreases to $16,600 per QALY gained when the mean time to PID is 12 months (0.022 QALY's gained, costing $370). Compared with 6-month screening, screening at 12-month intervals in high-risk patients has larger incremental cost-effectiveness ratios and is less effective through all PID development time, thus removing it from consideration for these patients because of extended dominance [43].

We examined many other possible PID risk distributions in sensitivity analyses, including uniform, declining exponential, declining linear, normal with broader or narrower widths, and square wave distributions. Cost-effectiveness results using these other distributions showed similar relative insensitivity to variation of PID development time. Considering 10-year time horizons and beginning screening in high-risk groups at age 15 decreased cost-effectiveness ratios, further favoring screening interventions. Age in itself had minimal effects; longer time horizons were most influential on results.

Results were most sensitive to variation of infection rate (Fig. 4). For each infection rate, the curves show the range of values seen as mean PID development time is varied from 1 to 12 months. As the yearly infection risk decreased below 5%, the range of values increased and became more economically unfavorable with greater absolute differences seen over the range of PID development time. When the yearly infection risk was 2.5%, the cost per QALY gained for 6-month screening was greater than $40,000 through the entire range of PID onset times, varying from $43,000 (12 months) to $72,700 (1 month). With infection risk at this lower level, 12-month screening had a cost per QALY gained $300–500 less than 6-month screening.

Varying most other variables in one-way sensitivity analyses had little impact on the magnitude or range of incremental cost-effectiveness ratios seen when PID development time was varied in high-risk women. For example, decreasing screening sensitivity to 65% increased incremental cost-effectiveness ratios by 33% to 40%: $23,300 per QALY if PID development time was 12 months or $42,400 per QALY if it was 1 month. Nevertheless, decreased screening costs had significant impact on results, decreasing cost-effectiveness ratios by more than half if screening costs were $40 or less. When screening sensitivity, screening cost, and yearly infection risk are varied in probabilistic sensitivity analyses over the ranges listed in Table 1 using triangular distributions, 6-month screening is strongly preferred; if societal willingness to pay is $50,000 per QALY gained, 6-month screening is preferred in 96.5% of model iterations if PID development time is 1 month and 100% of the time if development time is 6 or 12 months.

In sensitivity analyses, heterogeneity in PID development was examined in two ways. First, if yearly PID development risk is decreased to 1% (compared with 2.8% per year, or 10.9% over 4 years, in the base case), cost-effectiveness ratios increased by a factor

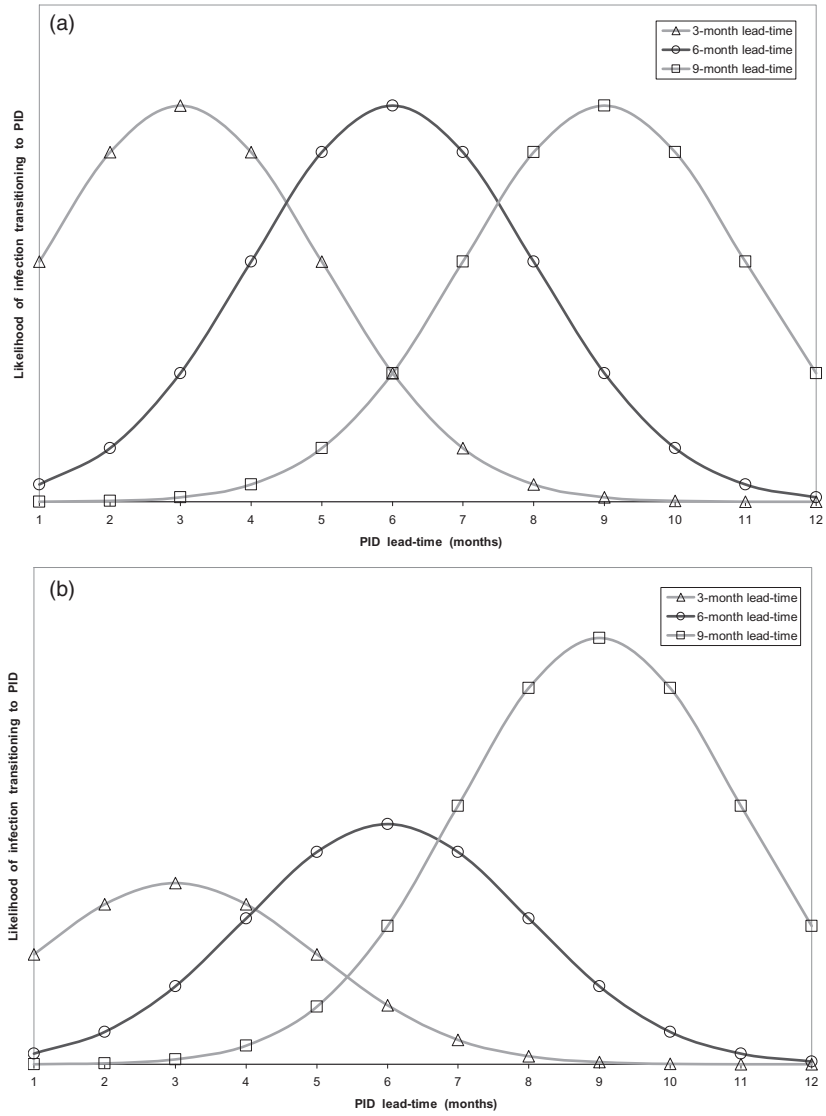

Figure 2 Risk distributions. (a) Truncated normal distributions for risk of progression from infection to pelvic inflammatory disease (PID). Similar distributions were used for other development time from 1 to 12 months, but are not shown. (b) Distributions were scaled to produce a 2.8%/year (or 10.9%/4 years) risk of progression from infection to PID when a 12-month screening program is in place, reproducing clinical trial results [15,23]. Distribution heights are smaller for shorter development time because of the effect of shorter development time causing more PID cases earlier in the 4-year time frame of the model.

of about 2.4 ($40,000–76,300 per QALY gained) throughout the range of PID development intervals. Second, if the baseline assumption of immediate PID risk in uncured symptomatically infected women is relaxed, with these women therefore developing PID at the same time intervals as the remainder of the infected population, cost-effectiveness ratios decrease by less than $1000 when calculated using either base-case or sensitivity analysis infection incidence rates.

Alternative model assumptions also had little influence on the effect that PID development time variation has on screening cost-effectiveness. If women were rescreened 3 to 4 months after infection as recommended for chlamydia infection by the CDC (3), then resumed 6-month screening after a negative screen, cost-effectiveness ratios decreased less than $1000 from baseline. Similarly, increasing STI risk after previous infection (to a 15% reinfection rate over 3 months) or increasing PID and complication risks after prior PID episodes (to a 25% greater relative risk than baseline values) had little influence on results compared with those found using base-case assumptions.

Discussion

In high-risk women, we found that the time from initial infection to the development of PID was a relatively minor factor in determining the cost-effectiveness of a 6-month combined chlamydia and gonorrhea screening strategy compared with a 12-month strategy. Nevertheless, the risk of infection, regardless of PID development time, was the most significant factor in changing cost-effectiveness results, with 6-month screening favored in high-risk women but becoming more unfavorable in lower-risk women, because of smaller gains in effectiveness being outweighed by higher costs from more frequent screening. Also, as infection or PID risks decreased, PID develop-

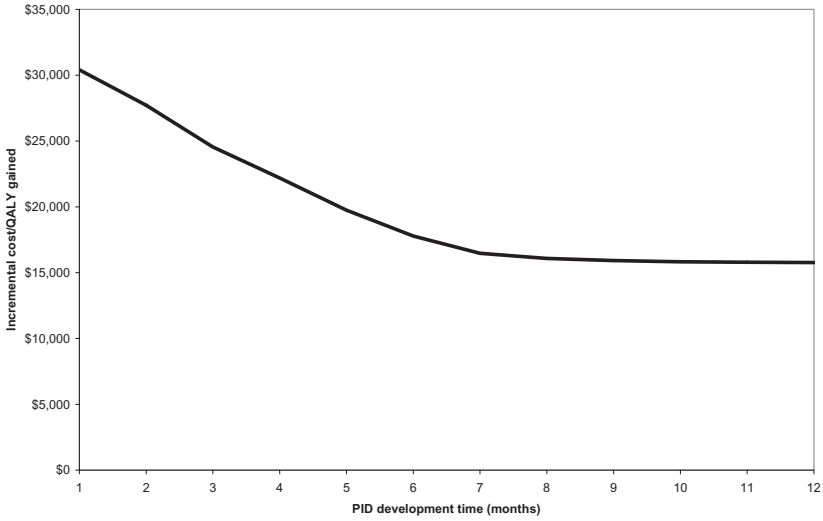

Figure 3 Results—cost-effectiveness. The incremental cost-effectiveness of 6-month screening compared with no screening as pelvic inflammatory disease (PID) development time varies from 1 to 12 months and all other parameters at baseline values as shown in Table 1. QALY, quality-adjusted life-year.

ment time became more important, with shorter development time making more frequent screening less economically favorable. Nevertheless, we found the magnitude of the interval between infection and PID development to be a significant factor when PID cases prevented are considered.

Given the inherent difficulties in measuring PID development time and the multifactorial complexity of its components, should there be further efforts to measure it? From an economic standpoint, the costs of obtaining better information would not be worthwhile when considering screening strategy choices in high-risk groups, given the relative insensitivity of the incremental cost-effectiveness ratio to variation of PID development time; the tension between biological plausibility and model complexity would seem to favor a simpler model in this patient group. For lower-risk populations, further attempts at measurement of PID development time might be reasonable based on absolute differences in cost-effectiveness ratios over the range of intervals studied. Nevertheless, given that, at best, costs per QALY are $43,000 or more for 6-month combined chlamydia and gonorrhea screening when the yearly infection risk is 2.5% or less, alternative screening strategies (screening for chlamydia only, less frequent screening, and/or further attempts at defining higher-risk subgroups) would be worth considering first in lower-risk groups. Further supporting this proposition is the difficulty inherent in attempting to disentangle the multiple factors and uncertainties surrounding the pathophysiology and epidemiology of PID. Nevertheless, modeling may allow estimation of PID development time if differences in PID rates between screening programs are available and the PID

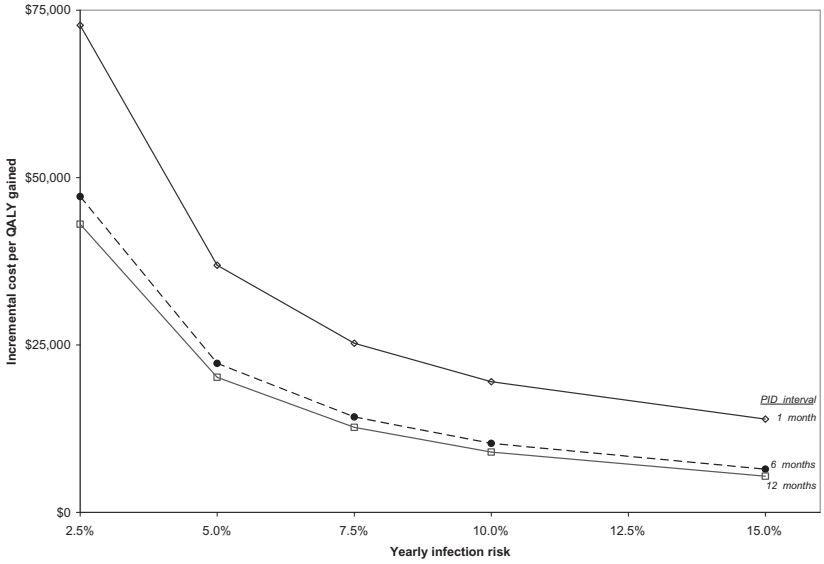

Figure 4 Sensitivity analysis—infection risk. Incremental cost-effectiveness ratio of 6-month screening with variation of pelvic inflammatory disease (PID) development time from 1 to 12 months (curves) and of yearly infection risks (*x*-axis). QALY, quality-adjusted life-year.

model can account for the many factors influencing PID development, including the PID risks of etiologic infections, the influence of recurrent infections, and the effects of age, race, sexual and other factors, and population infection prevalence.

Previous models have examined the cost-effectiveness of screening for chlamydia alone, finding this intervention cost-saving in high-risk young women [7,11] and costing less than $25,000 in lower-risk women less than 30 years old [12]. Our results tend toward higher costs, since we also include screening and treatment for gonorrhea, a less common infection, in our analysis and set high baseline costs for screening and treatment to bias the model against more frequent screening.

Our analysis has limitations. We did not model all possible infectious agents responsible for PID (e.g., anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram negative rods, *Streptococcus agalactiae*, cytomegalovirus, *Mycoplasma hominis*, and *Ureaplasma urealyticum*) separately. As a result, we did not account for etiologies other than chlamydia and gonorrhea in our model [13,22,24], perhaps overestimating the effects of screening. Nevertheless, decreasing screening sensitivity, one way of accounting for other infections, has little effect on cost-effectiveness results. Considering all infectious agents together in our theoretical model assumes similar infection characteristics, development time, and tendencies toward progression and complications, but not capturing the heterogeneity of the various etiologic agents. We did not consider the possible harms of more frequent screening: adverse effects of false positive screening on patients and partners, the inconvenience of obtaining test specimens, and the potential hazards of more frequent exposure to antibiotics. Finally, we used a static cohort model, not a dynamic population disease transmission model [8,11]. Our model was developed to test the importance of PID development time, an unmeasured and perhaps unmeasurable variable, and is a preliminary step in the development of a comprehensive model, which will consider dynamic population forces in STI incidence, prevalence, and spread, as well as other factors surrounding PID prevention and management. In this analysis, we found that screening high-risk young women for both chlamydia and gonorrhea every 6 months is economically reasonable and strongly favored over 12-month screening, but these results should be considered preliminary, based on the underlying motivation and limitations of our present model. Finally, the base-case analysis assumes homogeneity of women's responses to STI. It is possible that modeling a more complex population, with some subgroups developing PID relatively earlier than others, would alter results.

We conclude that, from a cost-effectiveness standpoint, time from infection onset to PID development is not a significant factor in screening interval choice for high-risk women. Nevertheless, PID development time could be important to consider in lower-risk groups. It appears that PID cost-effectiveness models for women at high STI risk may safely omit PID development time without significantly affecting results but, given its effect on PID cases prevented, more sophisticated modeling may be useful to estimate PID development time when changes in PID risk resulting from different screening intervals are known.

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